## CHAPTER 18

## ENDOCRINE ASSESSMENT

### INTRODUCTION

#### Background

The human endocrine system is not considered to be a major target of chlorophenol or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. This is not so in animals, however. A wide range of endocrine abnormalities in many animal species has been induced experimentally by TCDD and includes hypoglycemia,[1] hypothyroxinemia,[1,2] reduced progesterone levels,[3] and increased testosterone levels, the latter presumably reflecting decreased liver catabolism due to parenchymal liver damage or an inhibition of the cytochrome P-450 system.[4]

Extensive studies have been conducted on the interaction of TCDD with thyroid hormones in experimental animals. The exact nature of the interaction is still a matter of some discussion, but it is known that TCDD depresses the production and/or interaction of various thyroid hormones.[5-12] The effect on thyroid hormone-mediated metabolism of various compounds may be dependent on multiple hormones and may be the result of the alteration of receptor coupling or the number of receptors.[12-13] Hypoinsulinemia and hypoglycemia have been found to occur together in rats and may be an internal attempt to alter the toxic effects of TCDD.[14,15] The hypothalmus has been recently shown to also be a site of TCDD action in studies of dopamine.[16]

Extensive work with androgen levels in experimental animals has also been done. Studies consistently have shown a pronounced decrease in uterine estrogen (nuclear and cytosolic), progesterone (nuclear and cytosolic), and plasma testosterone and dihydrotestosterone following exposure to dioxin.[17-20] Hepatic and uterine estrogen receptor levels have shown a decrease after TCDD administration, and animals that do not maintain estrogen levels successfully (guinea pig and horse) show a much higher sensitivity to TCDD.[21,22] TCDD may alter the synthesis and release rate for androgens.[17]

Cholesterol metabolism suppression has also been shown with inhibition of cholesterol side-chain cleavage.[23,24] Further, thymic atrophy, one of the most sensitive indicators of TCDD toxicity in animals, has been shown not to be mediated by the pituitary-adrenal axis.[25] Comparable animal data for the isolated effects of 2,4-D and 2,4,5-T have been noticeably meager.

Other animal studies have emphasized the endocrine system, and thyroid function in particular, as important in causing or ameliorating TCDD toxicity, and not simply as an endpoint response.[26,27] Mounting experimental evidence suggests that both natural and radiation-induced hypothyroidism protect against TCDD lethality and that this favorable process can be quickly reversed by treatments with thyroxine ($T_4$).[28,29]

If the protective reaction of hypothyroidism in animals can be extrapolated to humans, it suggests that cases of hypothyroidism or altered patterns of thyroid hormones may aggregate in groups of highly exposed workers (particularly in those with chloracne) and, alternatively, that severe sequelae of TCDD exposure may be associated with hyperthyroidism. In fact, such thyroid findings have not been commonly reported in dioxin morbidity studies. Occasional cases of hypothyroidism and thyromegaly have been linked to exposures to polybrominated biphenyls and hexachlorobenzene, but the data were too sparse and oblique to support a causal relationship for hypothyroidism and TCDD exposure.[30,31] An assessment of the Times Beach, Missouri, residents, whose community was contaminated with TCDD, did not reveal thyroid stimulating hormone (TSH) or $T_4$ differences between the high- and low-risk groups.[32]

Temporary glycosuria and impaired glucose tolerance tests were noted in two studies of industrial workers exposed to TCDD.[33,34] However, neither abnormal glucose metabolism nor frank diabetes was specifically noted in other comparable studies.[35-38]

Overall, dioxin morbidity studies of humans have not rigorously assessed the clinical or biochemical parameters of the endocrine system. Detailed evaluations of endocrine function following TCDD exposure were included in the Air Force Health Study Baseline Morbidity Report and the 1985 followup report. Both reports are summarized below.

## Baseline Summary Results

A comprehensive biochemical assessment of the endocrine system was used for analysis in the Baseline examination in 1982.

Five measures of endocrine status were assessed: triiodothyronine percent ($T_3$ %) uptake, $T_4$, free thyroxine index (FTI), testosterone, and 2-hour postprandial glucose.

Results showed significant group differences for $T_3$ % uptake, predominantly in Ranch Hands 40 years old or less, and abnormally low $T_3$ % uptake values; the highest percentage of abnormalities was in those with high percent body fat. No group difference was noted for elevated 2-hour postprandial glucose values, and as expected, the prevalence of abnormal values was associated with older ages and higher percent body fat. Similarly, low testosterone levels were identical in both groups and were associated with increasing age and increasing percent body fat. Higher mean testosterone values (although still within normal range) were significantly more prevalent in the Ranch Hand group. Significant mean shifts were not noted for the $T_3$ % uptake, $T_4$, and FTI variables, although the $T_3$ % uptake was associated with a group-by-age interaction.

The exposure index analyses were essentially negative for the $T_3$ % uptake and $T_4$ variables. FTI, postprandial glucose, and testosterone analyses were marked by a series of covariate interactions in varying occupational categories. Of some note were the significant percent body fat-by-exposure interactions in two occupational strata in the glucose determination.

In summary, the endocrine system, as measured by five biochemical assays in 1982, did not reveal clinically apparent abnormalities that could be attributed to Herbicide Orange exposure. However, significant mean shifts in several values (although still in the normal range) presented trends, some of which were consistent with a herbicide etiology and others were counter to such an effort.

These data, coupled with the animal literature on the profound influence of the endocrine system on lethality and body fat metabolism following TCDD exposure, clearly underscored the importance of evaluating the endocrine system more comprehensively, as was done in the subsequent followup examinations.

## 1985 Followup Study Summary Results

Questionnaire and review-of-systems data for past thyroid disease were essentially equivalent in both the Ranch Hand and Comparison groups. These historical data were confirmed by medical record reviews. Physical examination findings were necessarily limited to data from palpation of thyroid glands and testicles; the unadjusted results showed no significant group differences.

Evaluation of the endocrine system was conducted primarily by laboratory testing of hormone levels. The thyroid test battery consisted of $T_3$ % uptake and TSH, as determined by radioimmunoassay (RIA) techniques. Testosterone, initial cortisol, differential cortisol (the difference between the initial and 2-hour cortisol levels), and 2-hour postprandial glucose levels were also analyzed. The $T_3$ % uptake data showed no group differences for either mean values or frequency of abnormally low or high values. Occupation was a significant covariate. TSH results revealed a significantly higher mean level in the Ranch Hand group, but this difference was not found by discrete analysis of the proportions of abnormally high TSH results.

The mean level of testosterone remained significantly elevated among Ranch Hands as contrasted with Comparisons in the 10 to 25 percent body fat category, but this was not reflected by the discrete analyses. For the few participants with less than 10 percent body fat (six Ranch Hands, four Comparisons), mean testosterone levels were lower for Ranch Hands than for Comparisons. Age, occupation, and percent body fat were significant adjusting variables.

Two timed cortisol specimens showed no significant group differences in mean values and percent abnormalities. The difference between the timed cortisol results, termed the differential cortisol, showed no significant group differences for nonblacks or Blacks born before 1942, but Black Ranch Hands born in or after 1942 had a lower mean differential cortisol level than did their Comparisons. Age, percent body fat, and personality type were significant covariates in these analyses.

Group means of 2-hour postprandial glucose levels were not statistically different, but discrete analyses revealed that there was a significantly higher frequency of glucose-impaired (at least 140 but less than 200 mg/dl) Comparisons than Ranch Hands. A constructed variable comprised of known diabetics and individuals classified as diabetic by the glucose tolerance test showed no difference between the Ranch Hand and Comparison groups. As expected, past and current diabetes were highly influenced by the covariates age, race, and percent body fat.

Exposure index analyses did not reveal any pattern consistent with a dose-response relationship. Enlisted flyers in the medium exposure level were significantly different from those in the low exposure level for 2-hour cortisol, differential cortisol, and 2-hour postprandial glucose. However, the corresponding high versus low contrasts were not statistically significant.

Longitudinal analyses of $T_3$ % uptake, TSH, and testosterone levels on all individuals attending both the Baseline and 1985 followup examinations revealed only symmetrical and nonsignificant changes in the Ranch Hand and Comparison groups in the interval between examinations.

In conclusion, both limited historical and physical examination data, seven endocrinologic laboratory variables, and a composite indicator of diabetes did not demonstrate consistent patterns indicating a herbicide effect. TSH and testosterone means tests were statistically significant, and in the expected direction of a herbicide effect. There was a significant interaction between group and percent body fat for testosterone that could be interpreted as a herbicide effect. These results were not confirmed by the discrete analyses. Also significant was the impaired category of the glucose tolerance test, which showed an excess in the Comparison group. The expected effects of age, race, occupation, and percent body fat on appropriate endocrine variables were consistently demonstrated. Overall, the endocrine health status was comparable in both groups.

## Parameters of the 1987 Endocrine Assessment

### Dependent Variables

Questionnaire, physical examination, and laboratory data were used in the endocrine assessment.

#### Questionnaire Data

In both the review-of-systems questionnaire and the health interval questionnaire, general screening questions on thyroid function and disease were posed to each participant. The review-of-systems questionnaire contained five questions on current thyroid function: thyroid or goiter trouble, high thyroid level, low thyroid level, lump in throat, and taking thyroid medication. Responses to these five questions were combined into a single item, which was coded as yes if there was a positive response to any question. During the face-to-face health interview, each study participant was asked, "Since the date of the last interview, has a doctor told you for the first time that you had thyroid problems?" A self-reported affirmative response to the interviewer-administered question was verified by medical record review and added to previously reported and verified information on the thyroid function for each participant. Based on the verified data, history of thyroid disease (interviewer-administered) was classified as yes/no. Responses from both the self-administered and interviewer-administered questions were analyzed as measures of the endocrine function.

Participants with a pre-Southeast Asia (SEA) history of thyroid disease, as determined by inteviewer-administered information, were excluded from the analysis of this variable.

### Physical Examination Data

The physical examination of the endocrine function was limited to manual palpation of the thyroid gland and the testes. Thyroid abnormalities consisted of enlarged gland, tenderness, or presence of nodules. The results of the testicular examination were coded as abnormal if atrophy was noted by the examiner.

Participants with thyroidectomies were excluded from the analysis of the thyroid gland. For the analysis of the testes, participants with orchiectomies were excluded.

### Laboratory Examination Data

The endocrine assessment from laboratory data consisted of the analysis of $T_3$ % uptake, TSH (μIU/ml), follicle stimulating hormone (FSH in μU/ml), testosterone (ng/dl), 2-hour postprandial glucose (mg/dl), and the composite diabetes indicator. The 100-gram glucose load for the postprandial assay was standardized by the use of Glucola®. The composite diabetes indicator was coded as yes for a verified history of diabetes or a 2-hour postprandial glucose greater than or equal to 200 mg/dl.

Except for the composite diabetes indicator, all laboratory variables were analyzed in both discrete and continuous forms. Continuous analyses for $T_3$ % uptake, TSH, FSH, and 2-hour postprandial glucose were done after transforming the data to the natural logarithm scale. A square root transformation was applied for all continuous analyses of testosterone. The cutpoints for the discrete analyses were based on Scripps Clinic and Research Foundation (SCRF) reference values. For the discrete analyses, $T_3$ % uptake and testosterone were initially to be coded as abnormal low, normal, and abnormal high. However, examination of the frequencies revealed sparse data for the abnormal low $T_3$ % uptake category and the abnormal high testosterone grouping. Only 22 participants had $T_3$ % uptake less than 25 percent (11 Ranch Hands, 11 Comparisons), and only 2 Ranch Hands and 3 Comparisons had testosterone levels greater than 1,250 ng/dl. Because of these sparse frequencies, the categories were collapsed with the respective normal classification for analysis. TSH was classified as normal/abnormal high. In the discrete analysis of 2-hour postprandial glucose, the results were coded as normal, impaired, and diabetic.

Participants with thyroidectomies or those taking thyroid medication were excluded from the analysis of $T_3$ % uptake and TSH. For testosterone, participants with orchiectomies or taking testosterone medication were excluded. Known diabetics (verified history) were excluded from the analysis of 2-hour postprandial glucose. Participants with a pre-SEA history of diabetes were excluded from the analyses of the composite diabetes indicator. No participants were excluded from the analyses of FSH.

**Covariates**

The effects of the covariates age, race, occupation, and personality type were examined in the assessment of the endocrine function, both in pairwise associations with the dependent variables and in adjusted statistical analyses. Personality type was not used for the adjusted analysis of FSH. In the adjusted analyses of testosterone, 2-hour post-prandial glucose, and the composite diabetes indicator, percent body fat was also a candidate covariate. Age and percent body fat were treated as continuous variables for all adjusted analyses. These variables were categorized for presentation of the covariate tests of association in Table 0-1 and for interaction exploration.

Personality type was determined from the Jenkins Activity Survey administered at the 1985 followup examination. This variable was derived from a discriminant function equation based on questions that best discriminate men judged to be Type A from those judged as Type B. Positive scores reflect the Type A direction and negative scores the Type B direction. This variable was dichotomized into Type A and Type B for all analyses. Participants at the 1987 followup examination who did not attend the 1985 followup examination had missing information for this covariate, as well as a few participants who could not be classified in 1985.

Percent body fat, a measure of the relative body mass[39] of an individual derived from height and weight recorded at the physical examination, was computed by the following formula:

$$\text{Percent Body Fat} = \frac{\text{Weight (kg)}}{[\text{Height (m)}]^2} \cdot 1.264 - 13.305.$$

In its discrete form, this variable was dichotomized as lean/normal ($\leq$25%) and obese (>25%).

**Relation to Baseline and 1985 Followup Studies**

All variables analyzed in the 1987 followup study except FSH were analyzed in the 1985 followup study. Of the variables analyzed in the 1987 followup, only $T_3$ % uptake, 2-hour postprandial glucose, and testosterone were analyzed at Baseline.

Three variables were analyzed in the longitudinal analysis of the endocrine function: $T_3$ % uptake, TSH, and testosterone.

**Statistical Methods**

The basic statistical analysis methods used in the assessment of the endocrine function are described in Chapter 7. Table 18-1 lists the dependent variables, data source, data form(s) (discrete and/or continuous), cutpoints, candidate covariates, and statistical methods used in the evaluation of the endocrine system. Additional information on the candidate covariates is provided in the second part of the table. Abbreviations are used extensively in the body of the table and are defined in footnotes.

**TABLE 18-1.**

**Statistical Analysis for the Endocrine Assessment**

**Dependent Variables**

| Variable (Units) | Data Source | Data Form | Cutpoints | Candidate Covariates | Statistical Analyses |
|---|---|---|---|---|---|
| Current Thyroid Function (Self-Administered) | Q-SR | D | Normal<br>Abnormal | -- | UC:FT |
| History of Thyroid Disease (Interviewer-Administered) | Q-V | D | Yes<br>No | -- | UC:FT |
| Thyroid Gland | PE | D | Normal<br>Abnormal | -- | UC:FT |
| Testes | PE | D | Normal<br>Abnormal | -- | UC:FT |
| $T_3$ % Uptake | LAB | D/C | Normal: ≤35%<br>Abnormal High: >35% | AGE<br>RACE<br>OCC<br>PERS | UC:FT,TT<br>AC:LR,GLM<br>CA:CC,TT,GLM, CS,FT<br>UE:GLM,TT<br>AE:GLM<br>L:RM |
| Thyroid Stimulating Hormone (TSH) (μIU/ml) | LAB | D/C | Normal: ≤3<br>Abnormal: >3 | AGE<br>RACE<br>OCC<br>PERS | UC:FT,TT<br>AC:LR,GLM<br>CA:CC,TT,GLM, CS,FT<br>UE:GLM,TT<br>AE:GLM<br>L:OR |
| Follicle Stimulating Hormone (FSH) (μU/ml) | LAB | D/C | Abnormal Low: <3<br>Normal: 3-18<br>Abnormal High: >18 | AGE<br>RACE<br>OCC | UC:CS,FT,TT<br>AC:LL,GLM<br>CA:CC,TT,GLM,CS<br>UE:GLM,TT<br>AE:GLM |
| Testosterone (ng/dl) | LAB | D/C | Abnormal Low: <260<br>Normal: ≥260 | AGE<br>RACE<br>OCC<br>PERS<br>%BFAT | UC:FT,TT<br>AC:LR,GLM<br>CA:CC,TT,GLM, CS,FT<br>UE:GLM,TT<br>AE:GLM<br>L:RM |

**TABLE 18-1. (continued)**

**Statistical Analysis for the Endocrine Assessment**

**Dependent Variables**

| Variable (Units) | Data Source | Data Form | Cutpoints | Candidate Covariates | Statistical Analyses |
|---|---|---|---|---|---|
| 2-Hour Post-prandial Glucose (mg/dl) | LAB | D/C | Normal: <140<br>Impaired: 140-<200<br>Diabetic: $\geq$200 | AGE<br>RACE<br>OCC<br>PERS<br>%BFAT | UC:CS,FT,TT<br>AC:LL,GLM<br>CA:CC,TT,GLM,CS<br>UE:GLM,TT<br>AE:GLM |
| Composite Diabetes Indicator | LAB | D | Yes: Verified History or glucose $\geq$200 mg/dl<br>No: Otherwise | AGE<br>RACE<br>OCC<br>PERS<br>%BFAT | UC:FT<br>AC:LR<br>CA:CS,FT<br>UE:CS,FT<br>AE:LR |

**Covariates**

| Variable (Abbreviation) | Data Source | Data Form | Cutpoints |
|---|---|---|---|
| Age (AGE) | MIL | D/C | Born $\geq$1942<br>Born 1923-1941<br>Born $\leq$1922 |
| Race (RACE) | MIL | D | Nonblack<br>Black |
| Occupation (OCC) | MIL | D | Officer<br>Enlisted Flyer<br>Enlisted Groundcrew |
| Personality Type (PERS) | PE (1985) | D | A Direction<br>B Direction |
| Percent Body Fat (%BFAT) | PE | D/C | Lean/Normal: $\leq$25%<br>Obese: >25% |

TABLE 18-1. (continued)

Statistical Analysis for the Endocrine Assessment

Abbreviations:

| | |
|---|---|
| Data Source: | LAB--1987 SCRF laboratory results<br>MIL--Air Force military records<br>PE--1987 SCRF physical examination<br>PE (1985)--1985 SCRF physical examination<br>Q-SR--1987 Family and Personal History questionnaire (self-reported)<br>Q-V--1987 NORC questionnaire (verified) |
| Data Form: | D--Discrete analysis only<br>D/C--Discrete and continuous analyses for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates |
| Statistical Analyses: | UC--Unadjusted core analyses<br>AC--Adjusted core analyses<br>CA--Dependent variable-covariate associations<br>UE--Unadjusted exposure index analyses<br>AE--Adjusted exposure index analyses<br>L--Longitudinal analyses |
| Statistical Methods: | CC--Pearson's product moment correlation coefficient<br>CS--Chi-square contingency table test<br>FT--Fisher's exact test<br>GLM--General linear models analysis<br>LL--Log-linear models analysis<br>LR--Logistic regression analysis<br>OR--Chi-square tests on the odds ratio<br>RM--Repeated measures analysis<br>TT--Two-sample t-test |

In addition to the medical exclusions discussed previously, some dependent variable and covariate data were missing. Table 18-2 summarizes missing and exclusionary data by group and variable.

## RESULTS

### Ranch Hand and Comparison Group Contrast

Unadjusted results for questionnaire and physical examination variables are presented in Table 18-3. Tables 18-4 and 18-5 summarize unadjusted and adjusted analysis results, respectively, for the laboratory examination variables. Pairwise associations between the laboratory examination variables and the candidate covariates are detailed in Appendix O, Table O-1. Table O-2 provides stratified results for analyses in which group-by-covariate interactions were found.

### Questionnaire Variables

#### Current Thyroid Function

As shown in Table 18-3, the response to self-administered questions relating to thyroid problems was not significantly different between groups (p=0.990 without adjustment for covariates).

#### History of Thyroid Disease

The percentage of participants who had a verified history of thyroid disease did not differ between groups in the unadjusted analysis (p=0.999).

### Physical Examination Variables

#### Thyroid Gland

The percentage of thyroid abnormalities was not significantly different between groups in the unadjusted analysis (p=0.914).

#### Testes

No significant unadjusted group difference was found for the testicular examination (p=0.999).

TABLE 18-2.

Number of Participants Excluded or With Missing Data for the Endocrine Assessment

| Variable | Analysis Use | Group: Ranch Hand | Group: Comparison | Total |
|---|---|---|---|---|
| Current Thyroid Function (Self-Administered) | DEP | 4 | 2 | 6 |
| $T_3$ % Uptake | DEP | 1 | 2 | 3 |
| TSH | DEP | 1 | 2 | 3 |
| FSH | DEP | 1 | 2 | 3 |
| Testosterone | DEP | 1 | 2 | 3 |
| 2-Hour Postprandial Glucose | DEP | 27 | 28 | 55 |
| Composite Diabetes Indicator | DEP | 5 | 7 | 12 |
| Personality Type (1985) | COV | 39 | 78 | 117 |
| Thyroidectomy | EXC | 11 | 11 | 22 |
| Currently Taking Thyroid Medication | EXC | 12 | 17 | 29 |
| Pre-SEA History of Thyroid Disease | EXC | 7 | 6 | 13 |
| Orchiectomy | EXC | 7 | 2 | 9 |
| Currently Taking Testosterone Medication | EXC | 1 | 0 | 1 |
| Verified History of Diabetes | EXC | 75 | 94 | 169 |
| Pre-SEA History of Diabetes | EXC | 3 | 3 | 6 |

Abbreviations: COV--Covariate (missing data)
DEP--Dependent variable (missing data)
EXC--Exclusion

**TABLE 18-3.**

**Unadjusted Analysis for Endocrinologic Questionnaire and Physical Examination Variables by Group**

| Variable | Statistic | Group: Ranch Hand | | Comparison | | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|
| Current Thyroid Function (Self-Administered) | n | 991 | | 1,297 | | | |
| | Number/% | | | | | | |
| | Abnormal | 41 | 4.1% | 55 | 4.2% | 0.98 (0.65,1.47) | 0.990 |
| | Normal | 950 | 95.9% | 1,242 | 95.8% | | |
| History of Thyroid Disease (Interviewer-Administered) | n | 988 | | 1,293 | | | |
| | Number/% | | | | | | |
| | Yes | 45 | 4.5% | 58 | 4.5% | 1.02 (0.68,1.51) | 0.999 |
| | No | 943 | 95.5% | 1,235 | 95.5% | | |
| Thyroid Gland | n | 984 | | 1,288 | | | |
| | Number/% | | | | | | |
| | Abnormal | 258 | 26.2% | 334 | 25.9% | 1.02 (0.84,1.23) | 0.914 |
| | Normal | 726 | 73.8% | 954 | 74.1% | | |
| Testes | n | 988 | | 1,297 | | | |
| | Number/% | | | | | | |
| | Abnormal | 33 | 3.3% | 44 | 3.4% | 0.98 (0.62,1.56) | 0.999 |
| | Normal | 955 | 96.7% | 1,253 | 96.6% | | |

## TABLE 18-4.

### Unadjusted Analysis for Endocrinologic Laboratory Examination Variables by Group

| Variable | Statistic | Group: Ranch Hand | Group: Comparison | Contrast | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|
| $T_3$ % Uptake | n | 975 | 1,273 | | | |
| | Mean[a] | 30.5 | 30.5 | | -- | 0.930 |
| | 95% C.I.[a] | (30.3,30.6) | (30.4,30.6) | | | |
| | Number/% | | | | | |
| | High | 39 4.0% | 45 3.5% | | 1.14 (0.73,1.76) | 0.640 |
| | Normal | 936 96.0% | 1,228 96.5% | | | |
| TSH (continuous) | n[b] | 813 | 1,051 | | | |
| | Mean[b] | 1.01 | 0.97 | | -- | 0.099 |
| | 95% C.I.[b] | (0.98,1.04) | (0.95,1.00) | | | |
| (below detection limit) | n | 975 | 1,273 | | | |
| | Number/% | | | | | |
| | ADL* | 813 83.4% | 1,051 82.6% | | --[c] | 0.648 |
| | BDL* | 162 16.6% | 222 17.4% | | | |
| (discrete) | n | 975 | 1,273 | | | |
| | Number/% | | | | | |
| | High | 20 2.1% | 24 1.9% | | 1.09 (0.60,1.99) | 0.894 |
| | Normal | 955 97.9% | 1,249 98.1% | | | |
| FSH | n | 994 | 1,297 | | | |
| | Mean[a] | 7.85 | 7.60 | | -- | 0.289 |
| | 95% C.I.[a] | (7.49,8.22) | (7.31,7.90) | | | |
| | Number/% | | | | | |
| | Low | 84 8.5% | 103 7.9% | Overall | | 0.192 |
| | Normal | 793 79.8% | 1,070 82.5% | Low vs. Normal/High | 1.07 (0.79,1.45) | 0.714 |
| | High | 117 11.8% | 124 9.6% | High vs. Normal/Low | 1.26 (0.97,1.65) | 0.102 |

**TABLE 18-4. (continued)**

**Unadjusted Analysis for Endocrinologic Laboratory Examination Variables by Group**

| Variable | Statistic | Group: Ranch Hand | Group: Comparison | Contrast | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|
| Testosterone | n | 986 | 1,295 | | | |
| | Mean[d] | 533.1 | 526.1 | | -- | 0.304 |
| | 95% C.I.[d] | (522.9,543.4) | (517.4,534.9) | | | |
| | Number/% | | | | | |
| | Low | 19 1.9% | 20 1.5% | | 1.25 (0.67,2.36) | 0.590 |
| | Normal | 967 98.1% | 1,275 98.5% | | | |
| 2-Hour Post-prandial Glucose | n | 915 | 1,198 | | | |
| | Mean[a] | 110.7 | 110.3 | | -- | 0.758 |
| | 95% C.I.[a] | (108.7,112.6) | (108.6,111.9) | | | |
| | Number/% | | | | | |
| | Normal | 750 82.0% | 995 83.1% | Overall | | 0.795 |
| | Impaired | 142 15.5% | 176 14.7% | Impaired vs. Normal | 1.07 (0.84,1.36) | 0.622 |
| | Diabetic | 23 2.5% | 27 2.3% | Diabetic vs. Normal | 1.13 (0.64,1.99) | 0.774 |
| Composite Diabetes Indicator | n | 987 | 1,288 | | | |
| | Number/% | | | | | |
| | Yes | 92 9.3% | 113 8.8% | | 1.07 (0.80,1.43) | 0.704 |
| | No | 895 90.7% | 1,175 91.2% | | | |

[a]Transformed from natural logarithm (log) scale.

--Estimated relative risk not applicable for continuous analysis of a variable.

[b]Transformed from log (X-0.4) scale; statistics based only on TSH values at or above detection limit of 0.5 µIU/ml.

*: ADL--Above detection limit; BDL--Below detection limit.

--[c]Analysis not done.

[d]Transformed from square root scale.

TABLE 18-5.

**Adjusted Analysis for Endocrinologic Laboratory Examination Variables by Group**

| Variable | Statistic | Group: Ranch Hand | Group: Comparison | Contrast | Adj. Relative Risk (95% C.I.) | p-Value | Covariate Remarks |
|---|---|---|---|---|---|---|---|
| $T_3$ % Uptake | n | 937 | 1,198 | | | | AGE (p=0.012) |
| | Adj. Mean[a] | 30.6 | 30.6 | | — | 0.941 | OCC (p<0.001) |
| | 95% C.I.[a] | (30.4,30.9) | (30.4,30.9) | | | | RACE*PERS (p=0.047) |
| | n | 975 | 1,273 | High vs. Normal | 1.14 (0.73,1.77) | 0.561 | AGE*RACE (p=0.011) |
| TSH | n[b] | 813 | 1,051 | | | | AGE (p<0.001) |
| | Adj. Mean[b] | 0.96 | 0.93 | | — | 0.092 | RACE (p=0.014) |
| | 95% C.I.[b] | (0.92,1.01) | (0.89,0.97) | | | | |
| | n | 975 | 1,273 | High vs. Normal | 1.09 (0.60,1.98) | 0.779 | — |
| FSH | n | 994 | 1,297 | | | | AGE (p<0.001) |
| | Adj. Mean[a] | 7.82 | 7.62 | | — | 0.290 | |
| | 95% C.I.[a] | (7.49,8.17) | (7.33,7.91) | | | | |
| | n | 994 | 1,297 | Low vs. Normal/High | 1.10 (0.81,1.51) | 0.523 | AGE (p<0.001) |
| | | | | High vs. Normal/Low | 1.23 (0.92,1.64) | 0.164 | |
| Testosterone | n | 986 | 1,295 | | | | AGE (p<0.001) |
| | Adj. Mean[c] | 532.4 | 526.6 | | — | 0.345 | %BFAT (p<0.001) |
| | 95% C.I.[c] | (523.4,541.5) | (518.8,534.5) | | | | |
| | n | 947 | 1,217 | Low vs. Normal | **** | **** | GRP*AGE (p=0.019) |
| | | | | | | | GRP*RACE (p=0.031) |
| | | | | | | | GRP*OCC (p=0.012) |
| | | | | | | | GRP*PERS(p=0.003) |
| | | | | | | | AGE*OCC (p=0.006) |
| | | | | | | | AGE*PERS (p=0.036) |
| | | | | | | | OCC*PERS (p<0.001) |
| | | | | | | | %BFAT (p<0.001) |

TABLE 18-5. (continued)

**Adjusted Analysis for Endocrinologic Laboratory Examination Variables by Group**

| Variable | Statistic | Group: Ranch Hand | Group: Comparison | Contrast | Adj. Relative Risk (95% C.I.) | p-Value | Covariate Remarks |
|---|---|---|---|---|---|---|---|
| 2-Hour Post-prandial Glucose | n | 878 | 1,122 | | — | 0.643 | AGE (p<0.001) |
| | Adj. Mean[a] | 111.1 | 110.5 | | | | OCC (p=0.001) |
| | 95% C.I.[a] | (109.2,113.0) | (108.8,112.3) | | | | %BFAT (p<0.001) |
| | | | | | | | PERS (p=0.042) |
| | n | 915 | 1,198 | Overall | | 0.679 | AGE (p<0.001) |
| | | | | Impaired vs. Normal | 1.09 (0.85,1.39) | 0.493 | OCC (p=0.002) |
| | | | | Diabetic vs. Normal | 1.19 (0.64,2.22) | 0.575 | %BFAT (p<0.001) |
| Composite Diabetes Indicator | n | 987 | 1,288 | | 1.10 (0.81,1.49)** | 0.533** | GRP*%BFAT (p=0.019) |
| | | | | | | | AGE*RACE (p=0.006) |
| | | | | | | | AGE*%BFAT (p=0.037) |
| | | | | | | | OCC*RACE (p=0.046) |

[a]Transformed from natural logarithm (log) scale.

—Adjusted relative risk not applicable for continuous analysis of a variable; no covariates significant in final model.

[b]Transformed from log (X-0.4) scale; statistics based only on TSH values at or above detection limit of 0.5 μIU/ml.

[c]Transformed from square root scale.

GRP: (Ranch Hand, Comparison).

****Group-by-covariate interaction (p≤0.01)—adjusted relative risk, confidence interval, and p-value not presented.

**Group-by-covariate interaction (0.01<p≤0.05)—adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

## Laboratory Examination Variables

### $T_3$ % Uptake

For the $T_3$ % uptake unadjusted analyses there was no statistically significant difference between Ranch Hand and Comparison group means (p=0.930) or the percentage of abnormal high values (p=0.640).

Using pooled group data, the covariate tests of association showed a highly significant relationship between $T_3$ % uptake and occupation (p<0.001). Table O-1 of Appendix O shows that the $T_3$ % uptake mean was highest for officers (30.9%), less for enlisted groundcrew (30.3%), and lowest for enlisted flyers (30.1%). None of the other covariates was significantly associated with $T_3$ % uptake.

Both the adjusted continuous and the discrete analysis did not detect a significant group difference (p=0.941, p=0.561, respectively). Significant covariates in the adjusted continuous model were a race-by-personality type interaction (p=0.047), and the main effects of age (p=0.012) and occupation (p<0.001). For the adjusted discrete model, the only significant term was an age-by-race interaction (p=0.011).

### TSH

The unadjusted continuous analysis for TSH consisted of two analyses because only TSH levels of 0.5 μIU/ml or more (82.9% of participants) could be accurately measured. First, the percentage of individuals with TSH levels less than the detection limit of 0.5 μIU/ml was compared between groups. This difference was not significant (p=0.648). Second, the group means for participants with values equal to and above the detection limit were compared. This difference approached statistical significance (p=0.099). The Ranch Hand group mean was 1.01 μIU/ml versus the Comparison group mean of 0.97 μIU/ml. The results of the unadjusted discrete analysis did not show a significant group difference (p=0.894).

Treating TSH as a continuous variable and pooling over groups, significant associations with age (p<0.001) and race (p=0.001) were found, along with a marginally significant association with occupation (p=0.062). These results are based only on participants with TSH values above the detection limit. The correlation with age was 0.173. The mean for nonblacks (1.00 μIU/ml) was higher than the mean for Blacks (0.87 μIU/ml). The means were 1.02 μIU/ml, 0.99 μIU/ml, and 0.96 μIU/ml for officers, enlisted flyers, and enlisted groundcrew, respectively.

Using data only from participants with TSH levels above the detection limit, the group difference based on the adjusted continuous analysis was marginally significant (p=0.092). The adjusted means were 0.96 μIU/ml and 0.93 μIU/ml for the Ranch Hands and Comparisons, respectively. Age (p<0.001) and race (p=0.014) were used for adjustment. No significant group difference was found for the adjusted discrete analysis (p=0.779). None of the candidate covariates or pairwise interactions between the covariates was included in the final adjusting model.

## FSH

For the unadjusted analyses of FSH, there were no statistically significant differences between Ranch Hand and Comparison group means (p=0.289), the percentage of abnormally low values (p=0.714), or the percentage of abnormally high values (p=0.102).

Using pooled group data, the covariate tests of association showed a highly significant relationship between FSH in its continuous form and age (p<0.001), between the percentage of participants having abnormally low FSH values and age (p<0.001), and between the percentage of participants having abnormally high FSH values and age (p<0.001). The correlation between FSH and age was 0.281. The percentages of participants having abnormally low FSH values among those born in or after 1942, between 1923 and 1941, and in or before 1922 were 11.1 percent, 6.3 percent, and 2.4 percent, respectively. The corresponding percentages of participants having abnormally high FSH values were 4.7 percent, 13.4 percent, and 33.3 percent, respectively.

There was a significant change in the FSH means due to race (p=0.016). The mean FSH levels for Blacks and nonblacks were 6.67 mU/ml and 7.78 mU/ml, respectively.

FSH means changed significantly with occupation (p<0.001); the means for officers, enlisted flyers, and enlisted groundcrew were 8.25 mU/ml, 7.99 mU/ml, and 7.18 mU/ml, respectively. There was a marginally significant association between the percentage of participants with abnormally low FSH values and occupation (p=0.056); the percentages for officers, enlisted flyers, and enlisted groundcrew were 6.8 percent, 7.3 percent, and 9.7 percent, respectively. There was a significant association between the percentage of participants having abnormally high FSH values and occupation (p<0.001); the percentages for officers, enlisted flyers, and enlisted groundcrew were 13.3 percent, 11.8 percent, and 7.7 percent, respectively.

In adjusted analyses of FSH, there was no significant group difference in means (p=0.290), the percentage of participants with abnormally high versus normal FSH levels (p=0.164), or the percentage of participants with abnormally low versus normal FSH levels (p=0.523). The only significant covariate in both the continuous and discrete analyses was age (p<0.001) for all analyses.

## Testosterone

No significant group difference was present for testosterone in either the unadjusted continuous (p=0.304) or discrete (p=0.590) analyses.

Covariate tests of association treating testosterone as a continuous variable revealed statistically significant or marginally significant relationships with all the candidate covariates. After discretizing testosterone, the only significant associations were with age (p<0.001) and percent body fat (p<0.001). A negative correlation with age was seen (r=-0.293, p<0.001). Correspondingly, the percentage of abnormally low values increased with age (1.3% for participants born in or after 1942, 1.7% for those born between 1923 and 1941, 7.1% for those born in or before 1922).

The testosterone means were 504.4 ng/dl, 529.6 ng/dl, and 550.3 ng/dl, for the officer, enlisted flyer, and enlisted groundcrew cohort, respectively ($p<0.001$). The correlation between testosterone and percent body fat was -0.366 ($p<0.001$); a much higher percentage of abnormally low levels was found for obese participants (4.2%) than for normal/lean participants (1.1%). The mean for personality Type B individuals (522.5 ng/dl) was lower than the mean for Type A participants (537.6 ng/dl, $p=0.031$). Nonblacks had a marginally lower mean than Blacks (527.6 ng/dl and 553.2 ng/dl, respectively; $p=0.078$).

For the adjusted continuous analysis, the Ranch Hand group mean was not significantly different from the Comparison group mean ($p=0.345$). Significant covariates included in the adjusted model were age ($p<0.001$) and percent body fat ($p<0.001$).

The results for the adjusted discrete analysis were not nearly as straightforward. Here, four group-by-covariate interactions were encountered (group-by-age, $p=0.019$; group-by-race, $p=0.031$; group-by-occupation, $p=0.012$; and group-by-personality type, $p=0.003$). To interpret these findings, the data were reanalyzed fitting separate adjusted models for each occupational cohort. No significant group difference was found for either officers ($p=0.765$) or enlisted flyers ($p=0.234$). The model for officers was adjusted for age ($p=0.010$) and percent body fat ($p<0.001$); the enlisted flyer model was adjusted for percent body fat ($p<0.001$) and personality type ($p=0.008$). For the enlisted groundcrew analysis, a group-by-age interaction ($p=0.009$) and a group-by-personality type interaction ($p=0.037$) existed. Categorizing age, unadjusted relative risks were derived for each of the six covariate combinations of age and personality type within the enlisted groundcrew cohort. Overall, there were 14 abnormally low enlisted groundcrew (7 Ranch Hands, 7 Comparisons). The basis of the interaction was partially attributable to the circumstance that the only three Type B Ranch Hand abnormals were all in the oldest age category. This contrasts with the Comparison group in which the five Type B abnormals were all found in the two younger age categories.

## 2-Hour Postprandial Glucose

Unadjusted group differences in 2-hour postprandial levels were not significant for the continuous and discrete analyses ($p=0.758$ and $p=0.795$, respectively).

Covariate tests of association using pooled group data revealed significant relationships between 2-hour postprandial glucose and age, occupation, percent body fat, and personality type. A positive correlation with age was found ($r=0.191$, $p<0.001$). This association was also highly significant after categorizing glucose levels ($p<0.001$). The highest percentage of participants with diabetic glucose levels was found for the middle age category (2.8%, born between 1923 and 1941); the highest percentage of participants with impaired glucose levels was found for the oldest age category (30.0%, born in or before 1922); and the highest percentage of participants with normal glucose levels was found for the youngest category (88.9%, born in or after 1942).

Of the occupational cohorts, the glucose mean was highest for the enlisted flyers (114.4 mg/dl). The means for the enlisted groundcrew and officers were 109.8 mg/dl and 109.5 mg/dl, respectively (p=0.024). Examination of the discrete test of association with occupation (p=0.004) showed the highest percentage of diabetic glucose level individuals in the enlisted groundcrew (3.3%), followed by enlisted flyers (2.0%) and officers (1.5%). The highest percentage of impaired glucose level individuals was found for the enlisted flyers (20.3%), followed by officers (14.1%), and enlisted groundcrew (13.9%).

The correlation between 2-hour postprandial glucose and percent body fat was 0.303 (p<0.001). Correspondingly, the percentage of diabetic glucose level participants was higher for obese men (6.7%) than normal/lean men (1.4%), as was the percentage of impaired individuals (24.4% and 12.8%, respectively; p<0.001). The mean for personality Type B participants was higher than the mean for Type A individuals (112.3 mg/dl and 108.4 mg/dl, respectively; p=0.004). Also, analysis of trichotomized 2-hour postprandial glucose revealed a marginally significant association (p=0.051). The percentage of Type B individuals with impaired glucose levels (17.0%) was higher than the corresponding percentage of Type A participants (13.1%); the percentages of diabetic participants were roughly equal (2.3% and 2.4% for Type A and Type B, respectively).

No significant group difference was found for both the adjusted continuous analysis (p=0.643) and the discrete analysis (p=0.679). The group difference in the continuous model was adjusted for age (p<0.001), occupation (p=0.001), percent body fat (p<0.001), and personality type (p=0.042). Age (p<0.001), occupation (p=0.002), and percent body fat (p<0.001) were used for adjustment in the final discrete model.

### Composite Diabetes Indicator

The percentage of Ranch Hands with a verified history of diabetes or a 2-hour postprandial glucose level greater than or equal to 200 mg/dl was not significantly different from the corresponding percentage of Comparisons in the unadjusted analysis (p=0.704).

Covariate tests of association showed highly significant relationships with age (p<0.001) and percent body fat (p<0.001). The percentage of diabetics increased with age (4.8%, 11.8%, and 14.5% for participants born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively). Obese individuals were much more likely to be diabetic than normal/lean individuals (20.3% and 6.0%, respectively).

The results of the adjusted analysis revealed a significant group-by-percent body fat interaction (p=0.019). Other significant covariates included in the model were interactions between age and race (p=0.006), age and percent body fat (p=0.037), and occupation and race (p=0.046). Stratified results showed a group relative risk marginally greater than 1 for normal/lean participants (Adj. RR: 1.40, p=0.093), in contrast to a relative risk less than 1 for obese participants (Adj. RR: 0.82, p=0.405). A second adjusted analysis was done ignoring the group-by-percent body fat interaction. The group difference was not significant for this analysis (p=0.533). Significant covariates used for adjustment in this analysis were an age-by-race interaction (p=0.033), an age-by-percent body fat interaction (p=0.044), and occupation (p=0.009).

## Exposure Index Analysis

### Laboratory Examination Variables

The exposure index analysis was done for the six laboratory examination variables. Except for the composite diabetes indicator, each was analyzed in its continuous form. Unadjusted and adjusted results are presented in Tables 18-6 and 18-7, respectively. Table 18-8 lists the exposure index-by-covariate interactions that were noted. Stratified results for these interactions are summarized in Table 0-3.

The final interpretation of these exposure index data must await the reanalysis of the clinical data using the results of the serum dioxin assay. The report is expected in 1991.

#### $T_3$ % Uptake

For each of the occupational cohorts, the unadjusted results of the $T_3$ % uptake were not significant. A significant exposure index-by-race interaction (p=0.022) was found for officers after covariate adjustment. Stratifying by race showed no significant differences among exposure categories for nonblack officers. For Black officers, the mean for the low exposure category was significantly less than the mean for the medium exposure category (p=0.008), and marginally less than the mean for the high exposure category (p=0.055). After excluding the interaction, the adjusted results were not significant. Adjusted results for the enlisted cohorts were not significant.

#### TSH

To account for the TSH detection limit problem discussed earlier, two sets of unadjusted exposure index analyses, comparable to the unadjusted core analysis, were done. The first analysis assessed the relationship between the proportion of detected values and the exposure index categories. For the officer cohort, a marginally significant difference between categories was seen (p=0.067). The percentage of undetectable observations (less than 0.5 µIU/ml) was highest for the low exposure group (20.2%), and lower for the other categories (11.2% and 11.5%, medium and high exposure, respectively). The medium versus low and high versus low contrasts were also marginally significant (p=0.071 and p=0.087, respectively). The results of this analysis were not significant for the enlisted cohorts. Using data only above or equal to the detection limit, the unadjusted means were not significantly different for any of the occupational cohorts. After covariate adjustment, a marginally significant difference was noted for the officer cohort (p=0.084). The adjusted means were 1.14 µIU/ml, 1.01 µIU/ml, and 1.17 µIU/ml for the low, medium, and high exposure categories, respectively. The medium versus low contrast was marginally significant (p=0.089).

**TABLE 18-6.**

**Unadjusted Exposure Index for Endocrine Variables by Occupation**

| Variable | Occupation | Statistic | Exposure Index: Low | Exposure Index: Medium | Exposure Index: High | Exposure Index Contrast | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|---|
| $T_3$ % Uptake | Officer | n | 129 | 118 | 122 | Overall | | 0.363 |
| | | Mean[a] | 30.9 | 31.1 | 30.6 | M vs. L | -- | 0.710 |
| | | 95% C.I.[a] | (30.5,31.4) | (30.6,31.5) | (30.2,31.1) | H vs. L | -- | 0.306 |
| | Enlisted Flyer | n | 55 | 63 | 50 | Overall | | 0.671 |
| | | Mean[a] | 30.2 | 30.0 | 30.5 | M vs. L | -- | 0.792 |
| | | 95% C.I.[a] | (29.3,31.0) | (29.5,30.6) | (29.8,31.1) | H vs. L | -- | 0.547 |
| | Enlisted Groundcrew | n | 146 | 153 | 139 | Overall | | 0.605 |
| | | Mean[a] | 30.5 | 30.2 | 30.2 | M vs. L | -- | 0.426 |
| | | 95% C.I.[a] | (30.1,30.9) | (29.9,30.6) | (29.8,30.6) | H vs. L | -- | 0.354 |

## TABLE 18-6. (continued)

## Unadjusted Exposure Index for Endocrine Variables by Occupation

| Variable | Occupation | Statistic | Exposure Index: Low | | Medium | | High | | Exposure Index Contrast | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TSH | Officer | n[b] | 103 | | 105 | | 108 | | Overall | | 0.208 |
| | | Mean[b] | 1.05 | | 1.01 | | 1.13 | | M vs. L | -- | 0.510 |
| | | 95% C.I.[b] | (0.96,1.16) | | (0.93,1.10) | | (1.03,1.26) | | H vs. L | -- | 0.279 |
| | | n | 129 | | 118 | | 122 | | Overall | | 0.067 |
| | | Number/% | | | | | | | | | |
| | | ADL* | 103 | 79.8% | 105 | 89.0% | 108 | 88.5% | M vs. L | --[c] | 0.071 |
| | | BDL* | 26 | 20.2% | 13 | 11.0% | 14 | 11.5% | H vs. L | --[c] | 0.087 |
| | Enlisted Flyer | n[b] | 43 | | 49 | | 44 | | Overall | | 0.652 |
| | | Mean[b] | 0.93 | | 1.02 | | 0.97 | | M vs. L | -- | 0.357 |
| | | 95% C.I.[b] | (0.84,1.04) | | (0.90,1.15) | | (0.84,1.15) | | H vs. L | -- | 0.659 |
| | | n | 55 | | 63 | | 50 | | Overall | | 0.317 |
| | | Number/% | | | | | | | | | |
| | | ADL* | 43 | 78.2% | 49 | 77.8% | 44 | 88.0% | M vs. L | --[c] | 0.999 |
| | | BDL* | 12 | 21.8% | 14 | 22.2% | 6 | 12.0% | H vs. L | --[c] | 0.282 |
| | Enlisted Groundcrew | n[b] | 120 | | 122 | | 119 | | Overall | | 0.471 |
| | | Mean[b] | 0.98 | | 0.94 | | 1.01 | | M vs. L | -- | 0.526 |
| | | 95% C.I.[b] | (0.90,1.06) | | (0.88,1.02) | | (0.93,1.12) | | H vs. L | -- | 0.554 |
| | | n | 146 | | 153 | | 139 | | Overall | | 0.419 |
| | | Number/% | | | | | | | | | |
| | | ADL* | 120 | 82.2% | 122 | 79.7% | 119 | 85.6% | M vs. L | --[c] | 0.696 |
| | | BDL* | 26 | 17.8% | 31 | 20.3% | 20 | 14.4% | H vs. L | --[c] | 0.534 |

**TABLE 18-6. (continued)**

**Unadjusted Exposure Index for Endocrine Variables by Occupation**

| Variable | Occupation | Statistic | Exposure Index: Low | Medium | High | Exposure Index Contrast | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|---|
| FSH | Officer | n | 130 | 124 | 124 | Overall | | 0.270 |
| | | Mean[a] | 8.25 | 9.49 | 8.46 | M vs. L | -- | 0.128 |
| | | 95% C.I.[a] | (7.28,9.35) | (8.28,10.86) | (7.44,9.61) | H vs. L | -- | 0.789 |
| | Enlisted Flyer | n | 55 | 63 | 53 | Overall | | 0.319 |
| | | Mean[a] | 7.10 | 8.59 | 8.60 | M vs. L | -- | 0.182 |
| | | 95% C.I.[a] | (5.75,8.76) | (7.10,10.39) | (6.95,10.66) | H vs. L | -- | 0.196 |
| | Enlisted Groundcrew | n | 147 | 158 | 140 | Overall | | 0.226 |
| | | Mean[a] | 6.74 | 6.92 | 7.73 | M vs. L | -- | 0.747 |
| | | 95% C.I.[a] | (6.01,7.56) | (6.26,7.65) | (6.73,8.87) | H vs. L | -- | 0.104 |
| Testosterone | Officer | n | 129 | 123 | 122 | Overall | | 0.032 |
| | | Mean[d] | 536.8 | 496.5 | 494.7 | M vs. L | -- | 0.024 |
| | | 95% C.I.[d] | (508.5, 565.8) | (474.0, 519.6) | (469.2, 520.9) | H vs. L | -- | 0.023 |
| | Enlisted Flyer | n | 55 | 62 | 53 | Overall | | 0.152 |
| | | Mean[d] | 531.7 | 550.5 | 491.5 | M vs. L | -- | 0.544 |
| | | 95% C.I.[d] | (490.3, 574.8) | (507.1, 595.8) | (451.0, 533.8) | H vs. L | -- | 0.201 |
| | Enlisted Groundcrew | n | 146 | 157 | 139 | Overall | | 0.218 |
| | | Mean[d] | 547.5 | 576.7 | 542.8 | M vs. L | -- | 0.168 |
| | | 95% C.I.[d] | (519.0, 576.8) | (550.9, 603.2) | (513.8, 572.6) | H vs. L | -- | 0.818 |

**TABLE 18-6. (continued)**

**Unadjusted Exposure Index for Endocrine Variables by Occupation**

| Variable | Occupation | Statistic | Exposure Index: Low | Exposure Index: Medium | Exposure Index: High | Exposure Index Contrast | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|---|
| 2-Hour Postprandial Glucose | Officer | n | 119 | 116 | 108 | Overall | | 0.639 |
| | | Mean[a] | 108.3 | 111.6 | 110.3 | M vs. L | -- | 0.350 |
| | | 95% C.I.[a] | (103.8, 112.9) | (106.5, 116.9) | (105.2, 115.7) | H vs. L | -- | 0.564 |
| | Enlisted Flyer | n | 54 | 56 | 51 | Overall | | 0.550 |
| | | Mean[a] | 109.5 | 114.6 | 116.0 | M vs. L | -- | 0.401 |
| | | 95% C.I.[a] | (101.8, 117.8) | (105.9, 124.2) | (107.5, 125.1) | H vs. L | -- | 0.306 |
| | Enlisted Groundcrew | n | 137 | 144 | 130 | Overall | | 0.875 |
| | | Mean[a] | 111.1 | 110.1 | 109.2 | M vs. L | -- | 0.782 |
| | | 95% C.I.[a] | (106.6, 115.9) | (105.0, 115.4) | (103.6, 115.1) | H vs. L | -- | 0.606 |

TABLE 18-6. (continued)

Unadjusted Exposure Index for Endocrine Variables by Occupation

| Variable | Occupation | Statistic | Exposure Index: Low | | Medium | | High | | Exposure Index Contrast | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Composite Diabetes Indicator | Officer | n | 130 | | 124 | | 121 | | Overall | | 0.699 |
| | | Number/% | | | | | | | | | |
| | | Yes | 10 | 7.7% | 11 | 8.9% | 13 | 10.7% | M vs. L | 1.17 (0.48,2.86) | 0.910 |
| | | No | 120 | 92.3% | 113 | 91.1% | 108 | 89.3% | H vs. L | 1.44 (0.61,3.43) | 0.536 |
| | Enlisted Flyer | n | 55 | | 63 | | 53 | | Overall | | 0.007 |
| | | Number/% | | | | | | | | | |
| | | Yes | 1 | 1.8% | 10 | 15.9% | 2 | 3.8% | M vs. L | 10.19 (1.26,82.40) | 0.015 |
| | | No | 54 | 98.2% | 53 | 84.1% | 51 | 96.2% | H vs. L | 2.12 (0.19,24.07) | 0.972 |
| | Enlisted Groundcrew | n | 145 | | 156 | | 140 | | Overall | | 0.340 |
| | | Number/% | | | | | | | | | |
| | | Yes | 11 | 7.6% | 16 | 10.3% | 18 | 12.9% | M vs. L | 1.39 (0.62,3.11) | 0.544 |
| | | No | 134 | 92.4% | 140 | 89.7% | 122 | 87.1% | H vs. L | 1.80 (0.82,3.96) | 0.202 |

[a]Transformed from natural logarithm scale.

--Estimated relative risk not applicable for continuous analysis of a variable.

[b]Transformed from log (X-0.4) scale; statistics based on TSH values at or above detection limit of 0.5 μIU/ml.

*: ADL--Above detection limit; BDL--Below detection limit.

--[c]Analysis not done.

[d]Transformed from square root scale.

TABLE 18-7.

**Adjusted Exposure Index for Endocrine Variables by Occupation**

| Variable | Occupation | Statistic | Exposure Index: Low | Medium | High | Exposure Index Contrast | Adj. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|---|
| $T_3$ % Uptake | Officer | n | 121 | 115 | 115 | Overall | | 0.314** |
| | | Adj. Mean**[a] | 31.0 | 31.1 | 30.6 | M vs. L | — | 0.694** |
| | | 95% C.I.**[a] | (30.0,32.1) | (30.1,32.2) | (29.6,31.7) | H vs. L | — | 0.279** |
| | Enlisted Flyer | n | 53 | 63 | 48 | Overall | | 0.494 |
| | | Adj. Mean[a] | 30.9 | 30.5 | 31.0 | M vs. L | — | 0.378 |
| | | 95% C.I.[a] | (29.8,32.1) | (29.5,31.5) | (30.0,32.2) | H vs. L | — | 0.804 |
| | Enlisted Groundcrew | n | 143 | 147 | 132 | Overall | | 0.695 |
| | | Adj. Mean[a] | 30.6 | 30.4 | 30.5 | M vs. L | — | 0.395 |
| | | 95% C.I.[a] | (30.1,31.1) | (29.9,30.9) | (30.0,31.0) | H vs. L | — | 0.639 |
| TSH | Officer | n[b] | 98 | 102 | 102 | Overall | | 0.084 |
| | | Adj. Mean[b] | 1.14 | 1.01 | 1.17 | M vs. L | — | 0.089 |
| | | 95% C.I.[b] | (0.92,1.44) | (0.84,1.25) | (0.95,1.47) | H vs. L | — | 0.734 |
| | Enlisted Flyer | n[b] | 41 | 49 | 42 | Overall | | 0.372 |
| | | Adj. Mean[b] | 0.80 | 0.90 | 0.88 | M vs. L | — | 0.180 |
| | | 95% C.I.[b] | (0.67,1.00) | (0.74,1.14) | (0.73,1.09) | H vs. L | — | 0.294 |
| | Enlisted Groundcrew | n[b] | 117 | 118 | 113 | Overall | | 0.638 |
| | | Adj. Mean[b] | 0.93 | 0.90 | 0.95 | M vs. L | — | 0.581 |
| | | 95% C.I.[b] | (0.84,1.03) | (0.81,1.00) | (0.86,1.06) | H vs. L | — | 0.686 |

TABLE 18-7. (continued)

Adjusted Exposure Index for Endocrine Variables by Occupation

| Variable | Occupation | Statistic | Exposure Index: Low | Exposure Index: Medium | Exposure Index: High | Exposure Index Contrast | Adj. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|---|---|---|
| FSH | Officer | n | 130 | 124 | 124 | Overall | | 0.562 |
| | | Adj. Mean[a] | 8.68 | 9.15 | 8.31 | M vs. L | — | 0.561 |
| | | 95% C.I.[a] | (7.66,9.84) | (8.06,10.39) | (7.32,9.43) | H vs. L | — | 0.626 |
| | Enlisted Flyer | n | 55 | 63 | 53 | Overall | | 0.194 |
| | | Adj. Mean[a] | 6.98 | 8.88 | 8.41 | M vs. L | — | 0.081 |
| | | 95% C.I.[a] | (5.72,8.53) | (7.37,10.71) | (6.86,10.30) | H vs. L | — | 0.194 |
| | Enlisted Groundcrew | n | 147 | 158 | 140 | Overall | | 0.374 |
| | | Adj. Mean[a] | 6.67 | 7.24 | 7.43 | M vs. L | — | 0.296 |
| | | 95% C.I.[a] | (5.95,7.47) | (6.49,8.08) | (6.61,8.34) | H vs. L | — | 0.184 |
| Testos-terone | Officer | n | 121 | 120 | 115 | Overall | | 0.300 |
| | | Adj. Mean[c] | 496.6 | 475.5 | 473.5 | M vs. L | — | 0.201 |
| | | 95% C.I.[c] | (446.2,549.7) | (427.4,526.3) | (424.5,525.1) | H vs. L | — | 0.161 |
| | Enlisted Flyer | n | 53 | 62 | 51 | Overall | | 0.049 |
| | | Adj. Mean[c] | 538.1 | 584.7 | 517.0 | M vs. L | — | 0.101 |
| | | 95% C.I.[c] | (477.8,602.0) | (526.1,646.3) | (460.2,577.1) | H vs. L | — | 0.449 |
| | Enlisted Groundcrew | n | 143 | 150 | 132 | Overall | | 0.785 |
| | | Adj. Mean[c] | 568.0 | 579.5 | 567.9 | M vs. L | — | 0.545 |
| | | 95% C.I.[c] | (535.2,601.8) | (545.8,614.1) | (533.2,603.7) | H vs. L | — | 0.994 |

TABLE 18-7. (continued)

**Adjusted Exposure Index for Endocrine Variables by Occupation**

| | | | Exposure Index | | | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | Occupation | Statistic | Low | Medium | High | Exposure Index Contrast | Adj. Relative Risk (95% C.I.) | p-Value |
| 2-Hour Post-prandial Glucose | Officer | n | 111 | 113 | 102 | Overall | | 0.925 |
| | | Adj. Mean[a] | 106.9 | 107.3 | 106.0 | M vs. L | — | 0.900 |
| | | 95% C.I.[a] | (97.2,117.6) | (97.8,117.8) | (96.4,116.6) | H vs. L | — | 0.793 |
| | Enlisted Flyer | n | 52 | 56 | 49 | Overall | | 0.679 |
| | | Adj. Mean[a] | 109.3 | 114.3 | 113.9 | M vs. L | — | 0.437 |
| | | 95% C.I.[a] | (96.0,124.4) | (101.3,129.1) | (100.2,129.6) | H vs. L | — | 0.463 |
| | Enlisted Groundcrew | n | 135 | 137 | 123 | Overall | | 0.907 |
| | | Adj. Mean[a] | 111.8 | 112.4 | 110.8 | M vs. L | — | 0.859 |
| | | 95% C.I.[a] | (105.5,118.4) | (105.8,119.5) | (104.1,117.9) | H vs. L | — | 0.789 |
| Composite Diabetes Indicator | Officer | n | 122 | 121 | 114 | Overall | | 0.575 |
| | | | | | | M vs. L | 0.76 (0.29,1.98) | 0.573 |
| | | | | | | H vs. L | 1.25 (0.50,3.09) | 0.637 |
| | Enlisted Flyer | n | 53 | 63 | 51 | Overall | | 0.010** |
| | | | | | | M vs. L | 10.40 (1.21,89.14)** | 0.033** |
| | | | | | | H vs. L | 1.92 (0.17,22.14)** | 0.600** |
| | Enlisted Groundcrew | n | 142 | 149 | 133 | Overall | | 0.223** |
| | | | | | | M vs. L | 1.74 (0.71,4.29)** | 0.227** |
| | | | | | | H vs. L | 2.07 (0.87,4.93)** | 0.099** |

**Exposure index-by-covariate interaction ($0.01<p\leq0.05$)—adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

[a] Transformed from natural logarithm scale.

—Adjusted relative risk not applicable for continuous analysis of a variable.

[b] Transformed from log (X-0.4) scale; statistics based only on TSH values at or above detection limit of 0.5 μIU/ml.

[c] Transformed from square root scale.

**TABLE 18-8.**

**Summary of Exposure Index-by-Covariate Interactions From Adjusted Analyses for Endocrine Variables***

| Variable | Occupation | Covariate | p-Value |
|---|---|---|---|
| $T_3$ % Uptake | Officer | Race | 0.022 |
| Composite Diabetes Indicator | Enlisted Flyer | Race<br>Personality Type | 0.024<br>0.016 |
| Composite Diabetes Indicator | Enlisted Groundcrew | Percent Body Fat | 0.041 |

*Refer to Table 0-3 for a further investigation of these interactions.

**FSH**

No significant results were found for FSH in any of the occupational cohorts for either the unadjusted or adjusted analyses. Inspection of means and percentages revealed no patterns suggestive of an exposure effect.

**Testosterone**

For officers, the unadjusted testosterone means for the three exposure categories were significantly different, exhibiting a decreasing dose-response effect (536.8 ng/dl, 496.5 ng/dl, and 494.7 ng/dl for the low, medium, and high exposure categories, respectively; p=0.032). However, after covariate adjustment, this finding was not significant (p=0.300). For enlisted flyers, the unadjusted results were not significant (p=0.152), but a significant difference was found for the adjusted analysis (p=0.049). The adjusted enlisted flyer mean was highest for the medium exposure category (584.7 ng/dl). The adjusted means were 538.1 ng/dl and 517.0 ng/dl for the low and high exposure categories, respectively. Unadjusted and adjusted results for the enlisted groundcrew were not significant.

**2-Hour Postprandial Glucose**

No significant results were found for any of the occupational cohorts for 2-hour postprandial glucose in either the unadjusted or adjusted analysis.

**Composite Diabetes Indicator**

For the unadjusted analysis, the percentage of diabetics differed significantly among exposure categories for enlisted flyers (p=0.007). A much higher percentage of diabetics was found in the medium exposure category (15.9%) than in either the low exposure category (1.8%) or the high exposure category (3.8%). Of the 13 diabetic enlisted flyers, 10 were from the medium exposure group. Exposure index interactions with race (p=0.024) and personality type (p=0.016) were found in the adjusted analysis. Unadjusted results, stratified by pairwise combinations for these covariates, are presented in Appendix O, Table O-3. Because the interaction p-values were greater than 0.01, further adjusted analysis was done excluding the interactions. A significant result, consistent with the unadjusted finding, was found for this analysis (p=0.010). The adjusted relative risk for the medium versus low contrast was 10.40 (95% C.I.: [1.21,89.14], p=0.033).

The percentage of diabetic officers increased with the exposure index levels (7.7%, 8.9%, and 10.7% for the low, medium, and high exposure categories, respectively), but the overall association was not significant (p=0.699) and remained nonsignificant after covariate adjustment (p=0.575). Similarly, a nonsignificant increasing dose-response relationship was seen for enlisted groundcrew (p=0.340). The percentages were 7.6 percent, 10.3 percent, and 12.9 percent for the low, medium, and high categories, respectively. An exposure index-by-percent body fat interaction was found for the adjusted analysis (p=0.041). The percentage of diabetic obese enlisted groundcrew exhibited an increasing dose-response effect (6.5%, 22.2%, and 31.3% for the low, medium, and high exposure categories, respectively; p=0.046). The percentage of diabetic normal/lean enlisted groundcrew was not significantly different among exposure categories (p=0.926). The results of further adjusted analysis, ignoring the interaction, were not significant (p=0.223).

## Longitudinal Analysis

Three laboratory examination variables--$T_3$ % uptake, TSH, and testosterone--were investigated to assess longitudinal differences between the 1982 Baseline examination and the 1987 followup. $T_3$ % uptake and testosterone were treated as continuous variables, and TSH was categorized. The abnormal cutpoint for TSH was specific to each examination since laboratory technique varied. The cutpoints were 10.0 μIU/ml at Baseline, 7.5 μIU/ml for the 1985 followup, and 3.0 μIU/ml at the 1987 followup. Table 18-9 presents the percentages of Ranch Hands and Comparisons with abnormal and normal TSH levels for 1982, 1985, and 1987. Table 18-10 compares 1982 results with 1987 results for each group. Summary statistics and results for $T_3$ % uptake and testosterone are provided in Table 18-11.

No significant longitudinal differences were found between the Ranch Hand and Comparison groups. As shown in Table 18-11, testosterone means have dropped steadily from 1982 to 1987 for both groups. Initially, the Ranch Hand mean was 19.8 ng/dl larger than the Comparison group mean; for 1987, the difference narrowed to 10.7 ng/dl. This change was not significant (p=0.242). The mean $T_3$ % uptake was relatively constant over time, with both groups exhibiting a slight drop in 1985. The percentage of participants with abnormal TSH values was highest for both groups for 1987, but this may be attributable to the change in abnormal cutpoints as well as an indication of an overall increase in disease with the passage of time.

**TABLE 18-9.**

**Summary Statistics for the Longitudinal Analysis of TSH: 1982 Baseline, 1985 Followup, and 1987 Followup Examinations**

| Examination | Statistic | Group: Ranch Hand | | Group: Comparison | |
|---|---|---|---|---|---|
| 1982 Baseline | Number/% | | | | |
| | Abnormal | 7 | 0.8% | 9 | 0.8% |
| | Normal | 917 | 99.2% | 1,081 | 99.2% |
| 1985 Followup | Number/% | | | | |
| | Abnormal | 5 | 0.6% | 4 | 0.4% |
| | Normal | 898 | 99.4% | 1,068 | 99.6% |
| 1987 Followup | Number/% | | | | |
| | Abnormal | 19 | 2.1% | 21 | 1.9% |
| | Normal | 905 | 97.9% | 1,069 | 98.1% |

Note: Summary statistics for the 1982 Baseline and 1987 followup are based on 924 Ranch Hands and 1,090 Comparisons who participated in the 1982 Baseline and 1987 followup examinations. Summary statistics on 903 of these Ranch Hands and 1,072 of these Comparisons who also participated in the 1985 followup are also included for reference purposes only.

**TABLE 18-10.**

**Longitudinal Analysis of TSH: A Contrast of 1982 Baseline and 1987 Followup Examination Abnormalities**

| Group | 1982 Baseline Exam | 1987 Followup Exam: Abnormal | 1987 Followup Exam: Normal | Odds Ratio (OR)* | p-Value ($OR_{RH}$ vs. $OR_C$) |
|---|---|---|---|---|---|
| Ranch Hand | Abnormal | 6 | 1 | 13.00 | |
| | Normal | 13 | 904 | | |
| | | | | | 0.999 |
| Comparison | Abnormal | 8 | 1 | 13.00 | |
| | Normal | 13 | 1,068 | | |

*Odds Ratio: $\frac{\text{Number Normal Baseline, Abnormal 1987 Followup}}{\text{Number Abnormal Baseline, Normal 1987 Followup}}$

TABLE 18-11.

**Longitudinal Analysis of Selected Endocrine Variables: A Contrast of 1982 Baseline and 1987 Followup Examination Means**

| Variable | Examination | Group Means: Ranch Hand | Group Means: Comparison | p-Value (Equality of Differences) |
|---|---|---|---|---|
| $T_3$ % Uptake[a] | 1982 Baseline | 30.2 | 30.2 | 0.922 |
| | 1985 Followup | 27.8 | 27.7 | |
| | 1987 Followup | 30.5 | 30.5 | |
| Testosterone[b] | 1982 Baseline | 639.7 | 619.9 | 0.242 |
| | 1985 Followup | 596.5 | 574.7 | |
| | 1987 Followup | 532.2 | 521.5 | |

Note: Summary statistics for $T_3$ % uptake are based on 924 Ranch Hands and 1,090 Comparisons who participated in the 1982 Baseline and 1987 followup examinations. Testosterone summary statistics are based on 935 Ranch Hands and 1,109 Comparisons who were at both examinations. The sample sizes differ due to different exclusion criteria and missing data. P-value given is in reference to the hypothesis test involving 1982 Baseline and 1987 followup results. Summary statistics for the 1985 followup examination are for reference purposes only. These statistics are based on 903 Ranch Hands and 1,072 Comparisons for $T_3$ % uptake, and 912 Ranch Hands and 1,090 Comparisons for testosterone, who participated in all three examinations.

[a]Means transformed from the natural logarithm scale; hypothesis test performed on the natural logarithm scale.

[b]Means transformed from the square root scale; hypothesis test performed on the square root scale.

## DISCUSSION

The historical and laboratory data collected in the endocrine assessment provide a valid reflection of thyroid, gonadal, and pancreatic functions by indices that are well established in clinical practice.

As would be expected, comparison of the current historical data with those of the 1985 followup revealed an increase over time in the incidence of thyroid disease, with similar trends in both the Ranch Hand (n=55 in 1985 vs. n=93 in 1987) and Comparison (n=78 in 1985 vs. n=113 in 1987) groups.

An increase in the presence of thyroid nodules as a result of advancing age is well documented in autopsy and ultrasound studies. However, a decrease was detected in thyroid abnormalities in the 1987 followup (n=592 abnormal) versus the 1985 followup (n=773 abnormals). Prior to the 1987 examination, an attempt was made to reduce interobserver variability among the examining physicians by employing more uniform techniques of palpation and by defining more objective endpoints for palpable abnormalities. Comparison of the data revealed virtually identical trends in both the Ranch Hands (342 abnormal in 1985 vs. 258 abnormal in 1987; 34% vs. 26% incidence) and Comparisons (431 abnormal in 1985 vs. 334 abnormal in 1987; 33% vs. 26% incidence).

Though not reported in the endocrine assessment, several additional physical findings beyond simple palpation are recognized as relevant to the clinical evaluation of thyroid and gonadal function. Body habitus, ocular and integumentary signs, and deep tendon reflexes are among the variables that were included in the general health, neurological, and dermatologic examinations, and are reported in Chapters 9, 11, and 14, respectively.

Of the two laboratory variables used, the $T_3$ % uptake, though far less sensitive than the serum TSH, assumes importance as the only index common to all three physical examination cycles. In the current study, as in the Baseline and 1985 followup, no significant differences were detected between the Ranch Hand and Comparison groups. Further, the few covariate associations defined fail to document any consistent clinical trends over time.

In lacking a lower limit of normal, the RIA technique of serum TSH determination is not sensitive to hyperthyroid states. Nonetheless, the current 1987 followup data can be validly compared with those from the 1985 followup, which exhibited significant differences between Ranch Hands and Comparisons for both the unadjusted and adjusted analyses. For the 1987 followup, the Ranch Hand group was found to have TSH levels that were marginally higher than the TSH levels of the Comparisons in both the unadjusted and adjusted analyses (unadjusted: 1.01 µIU/ml vs. 0.97 µIU/ml; adjusted: 0.96 µIU/ml vs. 0.93 µIU/ml).

With respect to gonadal function, no significant group differences were found, and two established clinical correlations were confirmed. With advancing age, a gradual decline in serum testosterone levels would be expected and was evident only in those participants born in or before 1922.

The correlation between testosterone levels and obesity is less well defined. While extremes of obesity (i.e., in excess of 100% of ideal body weight) are usually associated with gonadal suppression, no consistent relationship has been defined between serum testosterone and percent body fat. Further, the apparent differences in serum testosterone levels may in fact reflect changes in sex hormone binding globulin rather than the biologically active-free fraction. Finally, the finding of slightly lower testosterone levels in Type B individuals is of doubtful clinical significance but consistent with the increased frequency of endomorphic body habitus in this personality type. The earlier examinations in this series found that the Ranch Hands had higher levels of testosterone than did the Comparisons, a difference that is no longer evident.

An expected incidence of overt diabetes mellitus and of glucose intolerance was documented in the current study with no significant group differences defined. In ambulatory medicine, the 2-hour postprandial blood sugar has replaced the traditional glucose tolerance test as a screen for diabetes. Consistent with the insulin resistance that occurs in Type II diabetes, strong covariate associations were defined relating glucose intolerance to age and percent body fat. Independent of weight, a 10-15 percent incidence of glucose intolerance will occur by age 70. For each decade over age 40, there is an increase in the 2-hour postprandial blood sugar of 10-15 mg percent, and an average increase of 5.0 mg percent per decade in the fasting blood sugar.

In summary, the results of the endocrine assessment confirmed numerous associations that would be expected in clinical practice, and no significant or clinically relevant group differences were found.

## SUMMARY

Table 18-12 summarizes the results of Ranch Hand and Comparison group contrasts for the 10 variables examined in 1987 to assess the endocrine system.

Two variables were constructed from the review-of-systems questionnaire and the health interval questionnaire to determine the thyroid status for each participant. No significant group difference was noted for both the self-administered response to current thyroid function and the interviewer-administered response to history of thyroid disease.

The thyroid gland and the testes were evaluated at the physical examination. The percentage of abnormalities did not differ significantly between groups for either organ.

Six laboratory examination variables were analyzed to assess current endocrine function: $T_3$ % uptake, TSH, FSH, testosterone, 2-hour postprandial glucose, and a composite diabetes indicator. Each variable was analyzed in continuous and discrete forms, except for the composite diabetes indicator, which was only analyzed discretely.

No significant unadjusted group differences were found for any of these variables. However, the Ranch Hand TSH mean was marginally significantly higher than the Comparison mean ($p=0.099$). A statistically significant TSH difference was noted in the 1985 followup. The only change in findings after adjustment for significant covariates was due to the presence of four group-by-covariate interactions for testosterone discretized. Initial stratification by occupation revealed no significant group differences for the officer and enlisted flyer cohorts. Further stratification by personality type and age for the enlisted groundcrew cohort detected no significant strata, but results from this analysis were limited due to sparse data in many cells (in several strata the abnormally low testosterone values were either all Ranch Hands or all Comparisons). Although no significant group differences were found for the laboratory test variables, the direction of the unadjusted results showed that Ranch Hands consistently had more abnormalities than Comparisons. Trends such as these are discussed in Chapter 21.

Results from the exposure index analyses generally did not support a herbicide effect. For $T_3$ % uptake, TSH, FSH, and 2-hour postprandial glucose,

**TABLE 18-12.**

**Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of Endocrine Variables**

| Variable | Unadjusted | | Adjusted | | Direction of Results |
|---|---|---|---|---|---|
| | Discrete | Continuous | Discrete | Continuous | |
| Questionnaire | | | | | |
| Current Thyroid Function (Self-Administered) | NS | -- | -- | -- | |
| History of Thyroid Disease (Interviewer Administered | NS | -- | -- | -- | |
| Physical Examination | | | | | |
| Thyroid Gland | NS | -- | -- | -- | |
| Testes | NS | -- | -- | -- | |
| Laboratory | | | | | |
| $T_3$ % Uptake | NS | NS | NS | NS | |
| TSH | NS | NS* | NS | NS* | RH>C |
| FSH | NS | NS | NS | NS | |
| Testosterone | NS | NS | **** | NS | |
| 2-Hour Postprandial Glucose | NS | NS | NS | NS | |
| Composite Diabetes Indicator | NS | -- | ** (NS) | -- | |

NS: Not significant ($p>0.10$).
--Analysis not performed or not applicable.
NS*: Borderline significant ($0.05<p\leq0.10$).
RH>C: More abnormalities, or higher mean value, in Ranch Hands.
****: Group-by-covariate interaction ($p\leq0.01$).
** (NS): Group-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Table 0-2 for a detailed description of this interaction.

there were no statistically significant findings. Unadjusted testosterone means differed significantly for the officer cohort, exhibiting a pattern consistent with a decreasing dose-response relationship; after covariate adjustment, this difference became nonsignificant. Adjusted results were significant for the enlisted flyer cohort, but did not indicate a dose-response effect since the highest levels were found in the medium exposed group. Testosterone results for the enlisted groundcrew were not significant. The enlisted groundcrew and officer cohorts showed increasing dose-response patterns for diabetes, but the association was not significant. In contrast, a significant result ($p=0.010$) was found for the enlisted flyer cohort but was due to most diabetics falling in the medium exposure category.

Longitudinal analyses for $T_3$ % uptake, TSH, and testosterone showed no significant group differences from the Baseline to the 1987 followup examination.

In conclusion, statistical analysis of the 10 endocrinologic variables did not reveal any significant group differences. The Ranch Hand TSH mean was marginally significantly higher than the Comparison mean; at the 1985 examination, a significant difference was found. Means for the other variables were very similar between groups. For all laboratory examination variables, the percentage of abnormalities was higher for the Ranch Hand group than for the Comparison group, but not statistically significant. The significant differences in testosterone and 2-hour postprandial glucose found in the 1985 examination were no longer evident.

## CHAPTER 18

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